REMARKS

Claims 11-69 and 72 are currently pending in this application after entry of this amendment. Claims 11-64 have been withdrawn from examination as being directed to non-elected subject matter. Claims 1-10, 70, 71 and 73 are cancelled by this amendment. Claims 65-69 and 72 are presently under consideration.

Claims 65-69 and 72 have been amended. Support for the recitation "wherein said macrophage surface receptor is a FPRL-1 receptor comprising SEQ ID NO:2 or a variant, mutant or fragment thereof having the same function" of claim 65 can be found throughout the specification, *inter alia*, at page 5, paragraph 1. Claims 66-69 and 72 have been amended to be dependent upon claim 65 (or upon claim 66 or claim 68, which depend upon claim 65).

No new matter has been added.

Objections to the Claims

Claims 1-9 and 65-71 are objected to because, according to the Examiner, these claims recite non-elected subject matter (receptors other than SEQ ID NO:2 and generically recited variants thereof).

Claims 1-9, 70 and 71 have been cancelled thereby making this objection moot with respect to these claims. Claim 65 (and claims 66-69 dependent thereon) has been amended to recite "wherein said macrophage surface receptor is a FPRL-1 receptor comprising SEQ ID NO:2 or a variant, mutant or fragment thereof having the same function"; thus, this objection has been obviated and must be withdrawn.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 6 and 70 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

Applicants disagree; however, in order to advance prosecution of certain embodiments of the invention, claims 6 and 70 have been cancelled without prejudice. Applicants reserve the right to prosecute of the cancelled claims in one or more continuation or divisional applications. In light of the above amendments, this rejection is moot.

Claims 1-5, 7-10, 65-69, 71 and 73 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

The Examiner contends that the specification, while being enabling for the recited methods wherein the FPRL-1 receptor comprises SEQ ID NO:2, does not reasonably provide enablement for the methods reciting variants, mutants or fragments of SEQ ID NO:2. The Examiner alleges that it would require undue experimentation to generate and possibly screen for activity the infinite number of derivatives recited in the claims.

As a preliminary matter, Applicants point out that claims 1-5, 7-10, 71 and 73 have been cancelled thereby making this rejection moot with respect to these claims. With respect to this Section 112 rejection of claims 65-69, Applicants disagree and do not acquiesce.

Applicants point out that Section 112 does not require that the number of all of the possible compositions falling within the scope of the method claims be sufficiently small so that all of them are obtainable within a realistic time frame. Rather Section 112 requires that those compositions which are desired to be used in the claimed methods, within the broad range of compositions covered by the claims can be obtained and used without undue experimentation.

Indeed, Applicants have provided sufficient guidance in the specification which, when combined with the routine methods commonly known in the art to generate such variants, mutants or fragments thereof having the same function of an FPRL-1 receptor comprising SEQ ID NO:2 in the claimed methods, renders routine the generation of variants, mutants or fragments thereof having the same function of an FPRL-1 receptor comprising SEQ ID NO:2 falling within the breadth of the claims.

As the Examiner indicated, variants, mutants or fragments of an FPRL-1 receptor comprising SEQ ID NO:2 such as substitutions, deletions or additions in the amino acid sequence or the nucleotide sequence that provide for functionally equivalent molecules can be made by methods known in the art. Such methods known in the art include synthetic or chemical means (*e.g.*, Maniatis, T. , 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Further, such variants, mutants or fragments can be tested for functional equivalency by methods known in the art, *e.g.*, binding assays.

Although variants, mutants or fragments thereof having the same function of an FPRL-1 receptor comprising SEQ ID NO:2 may involve preparation and screening of a large number of samples, given the teaching of the specification and level of skill in the art, *i.e.*, at least a level of doctorate, it involves routine procedures and does not require undue experimentation.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 USPQ 2d 1401, 1412 (Fed. Cir. 1992).

In view of the foregoing, Applicants respectfully submit that the claims are enabled under Section 112 and requests withdrawal of this rejection.

Rejections under 35 U.S.C. §102

Claims 1-4, 7-10, 65-68 and 71-73 are rejected under 35 U.S.C. §102(b) as being anticipated by Takano *et al.*, 1997, J. Exp. Med. 185:1693-1704 ("Takano *et al.*").

Applicants respectfully disagree with these rejections under 35 U.S.C. §102(b) and, for the reasons detailed below, submit that the subject matter of claims 1-4, 7-10, 65-68 and 71-73 is in no way anticipated by the cited reference.

To constitute an anticipation, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed..." *Structural Rubber Prod. Co. v. Park Rubber Co.*, U.S.P.Q.1264 (Fed. Cir. 1984). As detailed below, the cited reference neither describes nor enables the presently claimed subject matter.

The Present Claims

Claims 1-4, 7-10, 65-68, 71 and 73 have been cancelled; thus this rejection is moot with respect to these claims.

Claim 65 (and claims 66-68 and 72 dependent thereon) is directed to a method for determining whether a substance inhibits or reduces an inflammatory process in which a *macrophage is in a hyperactivated status* due to a differentially expressed macrophage surface receptor, comprising: (a) applying said substance to a test system which generates a measurable read-out upon modulation of said *macrophage surface receptor* or macrophage surface receptor function, wherein said macrophage surface receptor is a FPRL-1 receptor comprising SEQ ID NO:2 or a variant, mutant or fragment thereof having the same function; and (b) comparing the level of the read-out of the test system to a control level, wherein a difference in levels indicates the substance is an inhibitor or an activator of said macrophage surface receptor; and wherein the inhibitor of the macrophage surface receptor which is expressed on a higher level in said hyperactived macrophage or the activator of the

macrophage surface receptor which is expressed on a lower level in said hyperactived macrophage indicates the substance inhibits or reduces said hyperactivated status of said macrophage.

The Cited Reference

Takano *et al.* are directed to exploration of functions of LXA4 (p.1693, Summary, lines 2 to 3). Takano *et al.* disclose an anti-inflammatory action for LXA4 (p.1693, Summary, lines 18 to 19), *i.e., LXA4 inhibited neutrophil infiltration* in mouse ears (p.1693, summary line 9 to 11). Additionally, Takano *et al* provided evidence for cloning of a mouse receptor designated as LXA4R to which LXA4 should bind and should exert its anti-inflammatory action (page 1697, right column lines 3 to 19 and page 1701, Discussion, lines 1 to 6). On page 1702 right column, lines 27 to 33, Takano *et al.* disclose that LXA4R is a seven transmembrane spanning receptor which has an anti-inflammatory function when activated, *e.g.*, by LXA4. Thus, Takano *et al.* teach the skilled artisan that *LXA4 is a kind of activator for LXA4R* which exerts an anti-inflammatory function *in neutrophils*.

Novelty of Present Claims

In complete contrast, the present invention is directed to a method for determining whether a substance inhibits or reduces an inflammatory process in which a *macrophage is in a hyperactived status due to a differentially expressed macrophage surface receptor.* As shown in Examples 1 to 3 (pages 9 to 37), FPRL-1 receptor is such a receptor, and it is significantly up-regulated in said hyperactived macrophages of smokers suffering from COPD when compared to data obtained from healthy smokers. The present invention, for the first time discloses a *pro-inflammatory function of FPRL-1 receptor in macrophages* which could be linked to COPD and to a said hyperactivated macrophage. The claims as presently amended recite methods to obtain a substance which can reduce or inhibit such an inflammatory process by determining whether the substance can inhibit a receptor which is expressed on a higher level in said hyperactived macrophage like a FPRL-1 receptor type receptor comprising SEQ ID NO:2 or a variant, mutant or fragment thereof having the same function. A desired substance according to the present invention is for example an inhibitor of FPRL-1 which reduces its pro-inflammatory action.

Moreover, Applicants direct the Examiner's attention to Christophe T. *et al.* Phagocyte activation by Trp-Lys-Tyr-Met-Val-Met, acting through FPRL1/LXA4R, is not

affected by lipoxin A4. *Scand. J. Immunol. 56(5):470-6, 2002*, submitted herewith, which demonstrates for the first time that the anti-inflammatory action of LXA4 is not via FPRL1. In particular, Applicants direct the Examiner's attention to the Abstract:

> Lipoxin A4 (LXA4) has been shown to bind to the leucocyte formyl peptide receptor (FPR) homologue, FPRL1, without triggering the biological activities induced by other FPRL1 agonists. We investigated the direct effect of LXA4 as well as the effect on agonist-induced biological responses using transfected HL-60 cells expressing FPR, FPRL1 or FPRL2. LXA4 neither induced an intracellular rise in calcium in these transfectants nor affected the response induced by the peptide Trp-Lys-Tyr-Met-Val-Met (WKYMVM), an agonist that activates cells through FPRL1 and -2. Both agonists induced Erk-2 activation; however, the eicosanoid-induced activity was independent of FPRL1 and FPRL2. Moreover, LXA4 was unable to trigger neutrophil up-regulation of complement receptor 3 and respiratory burst, and it had no effect on the responses induced by triggering with WKYMVM. *We conclude that LXA4 is unable to affect the WKYMVM-induced signalling through FPRL1 and suggest that it acts through a receptor different from FPRL1. (emphasis added)*

Since Takano *et al.* disclose *LXA4, an activator of LXA4R* and its anti-inflammatory action in *neutrophils* it differs from the methods of the present invention relating to the pro-inflammatory action of *FPRL-1* and its consequences for the status of *macrophages* and therewith for diseases like COPD described in the specification and claimed.

Applicants submit that for the reasons cited above, the cited reference cannot and does not anticipate the claimed methods. Accordingly, the rejections based on Section 102(b) must be withdrawn.

Rejections under 35 U.S.C. §103

Claims 5 and 69 are rejected under 35 U.S.C. §103 as being obvious over Takano *et al.* in view of United States Patent 5,811,520 to Hawkins *et al.* ("Hawkins *et al.*"). The Examiner alleges that it would be *prima facie* obvious to modify the method of Takano *et al.* by substituting the PMA+LPS treated THP-1 cells of Hawkins *et al.*

The Present Claims

Claim 5 has been cancelled; thus this rejection is moot with respect to this claim.

Claim 69 (dependent upon claim 68 which is dependent upon claim 65) is directed to a method for determining whether a substance inhibits or reduces an inflammatory process in which a *macrophage is in a hyperactivated status* due to a differentially expressed macrophage surface receptor, comprising: (a) applying said substance to a test system which

generates a measurable read-out upon modulation of said *macrophage surface receptor* or macrophage surface receptor function, wherein said macrophage surface receptor is a FPRL-1 receptor comprising SEQ ID NO:2 or a variant, mutant or fragment thereof having the same function; and (b) comparing the level of the read-out of the test system to a control level, wherein a difference in levels indicates the substance is an inhibitor or an activator of said macrophage surface receptor; and wherein the inhibitor of the macrophage surface receptor which is expressed on a higher level in said hyperactived macrophage or the activator of the macrophage surface receptor which is expressed on a lower level in said hyperactived macrophage indicates the substance inhibits or reduces said hyperactivated status of said macrophage in which the test system is a cellular system comprising a MonoMac6 cell or a THP-1 cell, and wherein said cell is stimulated with phorbol 12-myristate 13-acetate and with a substance selected from the group consisting of LPS and smoke.

The Cited References

As discussed above, Takano *et al.* teach the skilled artisan that *LXA4 is a kind of activator for LXA4R* which exerts an anti-inflammatory function *in neutrophils*. Hawkins *et al.* merely that promonocytic cells such as MonoMac6 or THP-1 are differentiated into activated macrophages by PMA and LPS and play a role in inflammation.

Applicants respectfully disagree and submit that these rejections are in error, both as a matter of law and fact. The criterion for determination of obviousness is whether the prior art would have suggested the presently claimed methods and kits to one of ordinary skill in the art and whether the presently claimed methods and kits would have a reasonable expectation of success, viewed in light of the prior art. *E.g., In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1022 (Fed. Cir.) (because no prior art references suggested probing strategy using two fully-redundant probes to screen human genomic library, claimed DNA held to be non-obvious), *cert. Denied*, 502 U.S. 856 (1991).

As discussed above, since Takano *et al.* disclose *LXA4, an activator of LXA4R* and its anti-inflammatory action in *neutrophils* it teaches away from the methods of the present invention relating to the pro-inflammatory action of *FPRL-1* and its consequences for the status of *macrophages* and therewith for diseases like COPD described in the specification and claimed. Moreover, combination of Takano *et al.* with the teaching of Hawkins *et al.*

who disclose a model for activated macrophages would never suggest, teach or motivate those skilled in the art to create a method according to the present invention without knowledge of the present invention, *i.e.*, the link between hyperactivated macrophages, inflammatory processes like COPD and deregulated macrophage surface receptors like up regulated FPRL-1 receptor. Additionally, the disclosure of both references would never provide enough information to design a method for determining whether a substance inhibits or reduces an inflammatory process in which a macrophage is in a hyperactivated status due to a differentially expressed macrophage surface receptor. Thus, the skilled artisan would neither know that he/she should look for deregulated macrophage surface receptors nor would he/she know that a hyperactivated status of macrophages could be linked with COPD.

In light of the above-summarized teachings of Takano *et al.* and Hawkins *et al*, it is clear that these references alone or in combination fail to suggest, teach or support a reasonable expectation of success in using the present methods. In view of the foregoing, Applicants submit that this rejection based on Section 103 must be withdrawn.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. Applicants believe that each ground for rejection has been successfully overcome and that the application is in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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